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## **R1 ANS-2021-00781 CLEAN**

### **Reduction in post-operative pancreatic fistula with polyethylene glycol and recombinant human albumin sealant following stapled distal pancreatectomy**

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Polyethylene glycol sealant reduces pancreatic fistula

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## ABSTRACT

**Background:** Postoperative pancreatic fistula (POPF) remains a significant cause of morbidity in patients undergoing distal pancreatectomy (DP). The use of polyethylene glycol (PEG) and recombinant human albumin sealant gel applied to the transected pancreatic margin in DP may reduce POPF rates and was assessed.

**Methods:** A retrospective single centre cohort study of patient undergoing DP at an Australian high volume tertiary institution between January 2015 and January 2021. Rates of POPF in patients undergoing stapled pancreatic transection with PEG sealant were compared to other methods.

**Results:** A total of 54 cases were identified for analysis, with 16 undergoing stapled DP combined with staple line application of PEG (PEG group). Most patients in the control group had stapled DP 92% (35 of 38), with 47% (18 of 38) combined with a reinforcing buttress, with or without the use other glue types. Overall, 28 of 54 (52%) developed a POPF, with a significantly lower rate in the PEG group (3 of 16 vs. 25 of 38 in the Control group;  $P = 0.003$ ). Clinically significant Grade B/C POPF was lower in the PEG group (0 of 16 vs. 9 of 28 in the Control group;  $P = 0.045$ ), and patients in the PEG group had a shorter median (range) length of hospital stay (6 [4–14] days versus 10 [6–41] days  $P = 0.04$ ).

**Conclusion:** Stapled DP with the application of PEG and recombinant human albumin sealant to the transection line appears to be associated with a lower rate of clinically significant POPF.

## INTRODUCTION

Postoperative pancreatic fistula (POPF) is one of the most common and clinically significant complications following pancreatic surgery.<sup>1</sup> The prevalence of this complication remains particularly high following distal pancreatectomy (DP) or left-sided pancreatic resection.<sup>2</sup> The rate of clinically significant pancreatic fistula in large series approaches 20% regardless of a minimally invasive or open approach.<sup>3</sup> POPF can result in worsening long-term survival and lower rates of completion of adjuvant treatment following pancreatic resection.<sup>4</sup> Various methods of treating the pancreatic stump have been evaluated, however few have shown significant reductions in the rates of pancreatic leak or subsequent fistula.<sup>5-9</sup>

Tissue adhesives are commonly used following DP for management of the remnant pancreas and to aid closure of the pancreatic duct. However, a systematic review has failed to demonstrate a significant difference in the incidence of either POPF or overall morbidity.<sup>10</sup> Many brands of tissue sealants are currently marketed for a variety of clinical indications. The majority of sealants investigated for treatment of the pancreatic stump are either fibrin-based or albumin-based.<sup>11</sup> Other, cyanoacrylate based adhesives have also been approved for human use, but their benefits for preventing POPF are unknown.<sup>12, 13</sup>

There are animal models and in-vitro tests showing that the application of a polyethylene glycol (PEG)-based sealant leads to complete closure of the pancreatic duct after five days, where glutaraldehyde-based sealants, prevented closure of the duct.<sup>14</sup>

Progel Platinum™ (BD Australia, Macquarie Park, NSW, Australia), a polyethelene glycol-based adhesive mixed with recombinant human albumin components, has shown better sealing properties compared to other adhesive types in stopping air leaks following lung resection.<sup>15, 16</sup> A similar formulation, Tridyne™ (BD United States, Franklin Lakes, NJ, United states), has also been approved for use as a vascular sealant., including intra-abdominal applications.<sup>17</sup> The application of such a PEG and recombinant human albumin sealant, referred to in short as PEG sealant, to the staple line following pancreatectomy appears to have merit as a haemostatic agent and to seal against pancreatic leak.

The primary aim of this study was to compare the postoperative pancreatic fistula rates in patients who had a stapled distal DP with the application of a PEG-based sealant to the staple line, with patients who did not have the application of PEG sealant. We hypothesised that stapled DP with the application of PEG sealant to the transection line reduces clinically significant POPF.

## **PATIENTS AND METHODS**

This study was approved by the Human Research Ethics Committee at Austin Health, Melbourne, Australia (Approval number: LNR/15/Austin/321). Given the retrospective nature of the study, the ethics committee waived the need for patient consent.

We performed a single centre retrospective cohort study of adult (age >18 years) patients who underwent DP with or without splenectomy, for benign or malignant lesions in the body or tail of the pancreas between January 2015 and January 2021 Both

open and laparoscopic approaches were included. We excluded patients who underwent central pancreatic resections and those who had emergency DP due to trauma. We also excluded patients who had the pancreatic stump treated by pancreatojejunostomy. All surgeries were performed by specialist pancreatic and hepatobiliary surgeons.

### **Definitions and data collection**

Demographical data including age, gender, American Society of Anesthesiologists (ASA) classification, body mass index (BMI), associated medical conditions and blood tests were recorded.

POPF was classified according to the updated International Study Group of Pancreatic Surgery (ISGPS) criteria.<sup>18</sup> A pancreatic (Biochemical) leak was defined accordingly as a drain amylase level greater than 300 U/L (representing three times the upper normal limit for serum level at our institution). Drain amylase was measured on postoperative day three.

Postoperative complications and outcomes were recorded and graded according to Clavien-Dindo Classification.<sup>19</sup> In case of disagreement on grading by two assessors, the case was discussed with reference to the classification guide by a third assessor. Length of stay was determined by the period between surgery and hospital discharge, excluding days in the hospital-in-the-home unit. Readmission was defined as unplanned readmission to the hospital within a 28-day follow-up period.

### **Surgical procedures**

All procedures were performed by hepatobiliary and pancreatic trained specialist surgeons. All patients received intra-operative antibiotics and prophylactic heparin, unless contraindicated. The information recorded included operative technique, surgery duration and intraoperative complications. The control group of patients represented a heterogeneous group, comprising various methods of treating the pancreatic stump. The method of transection varied during the period, this included reinforced and non-reinforced stapling devices and the applications of different sealants. A change of transaction technique was instituted by one surgeon (MN) from December 2019 that involved pancreatic transection performed with a non-reinforced Endo GIA™ Black 60 mm tri-stapler (4.0mm – 5.0mm) (Medtronic Australasia Pty Ltd, North Ryde, NSW, Australia). Cautery was applied to the staple line only when additional haemostasis was needed. Following transection, haemostasis and drying the staple line with a piece of gauze, 4 ml of PEG recombinant human albumin component adhesive sealant (Progel Patinum™) was applied to the staple line. All patients had a surgical drain placed routinely and positioned intra-operatively adjacent to the pancreatic stump, with low-pressure suction applied.

### **Statistical analysis**

Results were expressed as median (range) unless otherwise stated. Comparisons between categorical variables were determined by chi-square or Fisher's exact test, where appropriate. Non-categorical variables were assessed by the Mann–Whitney U test. A statistical software package (IBM SPSS Statistics Version 27, New York, NY, USA) was used for statistical analysis, with p value  $\leq 0.05$  considered statistically significant. No sample size calculations were performed given the retrospective nature of the study.

## RESULTS

During the study period 62 distal pancreatectomies were performed. Eight patients were excluded from analysis (four completion pancreatectomies, one resection treated by a pancreatojejunostomy and three resections performed for emergency or traumatic indications), leaving 54 patients suitable for analysis. The patients requiring emergency DP all had inadvertent pancreatic injury during other operative interventions, with subsequent Grade B/C POPF, with none treated with PEG sealant.

### Patient characteristics

Of the 54 cases included for analysis, 16 patients had a stapled DP treated with polyethylene glycol sealant (PEG group). This group was compared with patients undergoing DP where the pancreatic stump was treated by other methods (Control group). Table 1 lists the characteristics of the patients in each group. There were no significant differences between the groups in terms of gender, age, body mass index (BMI) and ASA status. Laboratory tests shows that the albumin and creatinine levels were higher in the PEG group compared to the Control group. Values in both groups were within the normal laboratory range and not clinically significant.

### Operative and pathology details

Operative and pathology details are summarised in Table 2. Similar numbers of patients in each group had a laparoscopic DP (29% vs 38%). All patients in the PEG group had a splenectomy and 19% had a concurrent colectomy or liver resection. This was significantly greater in the PEG group compared to the Control group (P=0.02)

Among the 38 patients in the Control group, 35 patients had pancreatic parenchymal division with a linear stapler and 18 of these used a reinforced stapler. Two patients in the control group had purely a sutured closure of the pancreatic stump and one had division with a bipolar electro-surgical device. Inclusion of these patients did not alter the statistical significance of the results. In the control group, 19 patients had the addition of tissue adhesive sealant to manage the pancreatic stump, consisting of fibrin (n=15), albumin (n=3) or cyanoacrylate based (n=1) adhesives. No patient in the control group had a PEG adhesive. In the PEG group, PEG adhesive glue was applied to the staple line in a standard manner as previously described. No patients required suture placement at the staple line for haemostasis. The appearance of the staple line before and after PEG applications is shown in Figure 1. A transparent, and incorporated gel formed within a few minutes of adhesive application in all cases.

There was no significant difference in the pathology diagnosis of each group, with approximately a half of the cases performed for malignant disease and approximately 40% of cases exhibiting some element of chronic pancreatitis on histopathology assessment.

### **Postoperative complications**

Post-operative details and complications are outlined in Table 3. The overall complication rate in those treated with PEG was 25% (4 of 16) and was not statistically significantly different to the overall complications in the control group at 47% (18 of 38) ( $p = 0.15$ ). However, the rate of POPF was however significantly lower in the PEG group (3 of 16 (19%) versus 25 of 38 (65%)  $p = 0.003$ ). Importantly, there were no clinically significant cases of POPF in the PEG group, compared to nine cases (24%)

in the control group ( $p = 0.045$ ). The PEG group had median length of hospital stay of 6 (4-14) days, which was significantly shorter than the 10 (6-41) days noted in the control group ( $p = 0.04$ ). The use of PEG based sealant appeared to be the only factor contributing to a reduction in significant POPF. Age, gender, diabetes, chronic pancreatitis, pre-operative albumin and malignant pathology status were not associated with trends in changes in Grade B/C POPF rates, to warrant a multivariate analysis.

In a subgroup analysis of 19 patients treated with various adhesives in the control group, the rate of POPF of all grades was also significantly higher in this group compared to the PEG treatment group (11 of 19 (58%) versus 3 of 16 (19%)  $p = 0.04$ ). Four (21%) of the patients from the control group had a Grade B/C leak.

In a further subgroup analysis looking only at patients with stapled resection in the control group, the difference in POPF rates was also significant (23 of 35 (65%) vs 3 of 16 (19%)  $p = 0.002$ ). In the control group, nine patients were operated on by the surgeon responsible for all patients in the PEG group (MN). In this small subset of the control group, the rates of biochemical leak (33%) and Grade B/C POPF (33%) were comparable to the remainder of the control group.

## **DISCUSSION**

We performed a single centre retrospective analysis of patients undergoing DP and found that stapled DP with the application of PEG and recombinant human albumin sealant to the transection line is associated with a reduction in clinically significant POPF when compared to other methods. Various surgical techniques can be used to

transect the pancreas and manage the stump following DP. The incidence of POPF following DP remains high and is major cause of morbidity and is associated with reduced survival in pancreatic cancer, most likely through delaying or preventing the administration of adjuvant chemotherapy.<sup>4</sup> Improved techniques to reduce POPF are worthy of exploration..

Numerous techniques have been described to reduce the development of clinically relative POPF such as the use prophylactic pancreatic duct stenting, administration somatostatin analogues, performing a pancreatic-enteric anastomosis and the use of various electrosurgical transection methods.<sup>30-32</sup> The use of prophylactic pancreatic stenting may reduce leak rates in certain circumstances, but routine use has its own risks and cannot be advocated in all cases<sup>20</sup> It may be particularly be useful if there is the presence of a proximal benign proximal pancreatic duct stricture or in the setting of papillary stenosis We did not administer any somatostatin analogues in our series, although it may have a role in some circumstances. Most of the data on somatostatin analogues is however in the setting of pancreaticoduodenectomy and its potential benefits are offset against product costs.<sup>21</sup>

Stapled pancreatic transection is the most common technique used to divide and seal the pancreas. Reinforcing materials have been used as a buttress to improve the sealing effects of staples, with reduction in POPF noted in several studies.<sup>22-25</sup> In 2019, Konodo et al. published a multicentre randomized controlled trial involving 122 patients undergoing DP, showing no significant differences overall in clinically relevant POPF between reinforced and bare stapler groups (16.3% vs. 27.1%, P=0.15).<sup>26</sup> Following this publication, the use of reinforcement in DP was abandoned

in our unit, with one surgeon (MN) adopting bare stapled resection combined with PEG sealant, with 16 patients treated by this method during the study period.

The use of glues to treat the pancreatic transection site is not a new concept. There are various brands of tissue adhesive on the market, however meta-analyses of the use of glues in pancreatic surgery have failed to show significant reductions in POPF.<sup>11,27</sup> In our clinical experience, many sealant brands fail to firmly fuse with the pancreatic surface and once dried, can be peeled off from the tissue. This was not the case, however with the PEG-based sealant utilised. In animal studies, application of a PEG-based sealant leads to closure of the pancreatic duct after 5 days, while other, glutaraldehyde-based sealants, inhibited closure of the duct.<sup>14</sup> Similarly, fibrin based products showed complete dissolution in pancreatic juice where PEG based preparations did not.<sup>14</sup> This suggests that PEG may have superior properties in achieving a seal than other products. In fact, the use of some PEG based felt patches applied to the cut pancreatic surface has shown reductions in POPF in both retrospective studies and randomised controlled trials.<sup>28-31</sup> A recent randomised controlled trial utilising a collagen pad that is coated with PEG, showed reduction in complications when used to treat the pancreatic stump after DP, particularly after a hand-sewn closure. This study however did not show any significant reductions in Grade B/C POPF.<sup>32</sup> The application of a sealant or glue is technically easier than wrapping the pancreatic stump with a mesh or patch.

The benefits of PEG sealant were considered two-fold, potentially preventing the development of POPF and acting as a haemostatic agent. PEG sealant was used in 16 consecutive patients to treat the staple line after DP with no detectable clinically

relevant POPF. All cases had transection performed with a bariatric, extra-thick tri-staple stapler to minimise crushing the pancreatic stump. The staple height from outside to inside with this staple type measured 4.0mm, 4.5mm and 5mm. The splenic artery and vein were divided with a vascular stapling device, or suture ligated separately if possible. There is reliable evidence, particularly in the setting of reinforced stapler trials, that the thickness of the pancreas influences pancreatic leak rates, with pancreas thickness measuring more than 14 mm increasing the risk of a leak.<sup>26</sup>

In our series, three patients (19%) in the PEG group had a biochemical leak. Two of these patients had an extremely firm and thick pancreas with evidence of xanthogranulomatous chronic pancreatitis on histology. The third patient was severely malnourished and required multi-organ resection for a recurrent retroperitoneal sarcoma. Drain amylase level was 589 at day 3, with the drain removed a few days later. In the control group the overall the pancreatic leak rate was 65%, with 23% representing grade B/C POPF. Within this control group, 92% of patients had a stapled resection. These were all performed with either an Endo GIA™ tri-stapler (51%) or an Echelon powered stapler (49%). The staple line was reinforced in 47% of patients who had a stapled transection. Half of the patients in the control group had non-PEG based sealant applied. There was no significant difference between these groups. The overall median length stay was 4 days shorter for the PEG group compared to the control group, despite the overall complication rate being similar in both groups. It should be noted that a higher proportion of patients in the PEG group underwent multi-organ resection, but there was only one (6%) Clavien-Dindo grade 3 /4 complication compared with seven (18%) cases in the control group.

The study is limited by its retrospective nature, single-centre and the use of the PEG and recombinant albumin sealant by one surgeon. There are also some risk factors for POPF, such as pancreatic thickness, duct diameter and gland texture, that were not controlled for in this study, as they were not consistently recorded in the operative records.

The reduction in clinically significant POPF in the PEG group is extremely promising and warrants further prospective assessment and validation. Despite these limitations, the authors believe that this study demonstrates the safety and potential efficacy of PEG sealant to manage the pancreatic resection margin following stapled distal pancreatectomy in reducing POPF. A randomised controlled trial across multiple centres using PEG and recombinant human albumin sealant in the setting of stapled distal pancreatectomy is required to validate the findings of this study.

**LEGEND**

Figure 1: Appearance of the stapled pancreatic transection prior (A) and a few minutes following (B) polyethylene glycol sealant application. A firmly incorporated transparent film forms over the staple line and pancreatic stump.

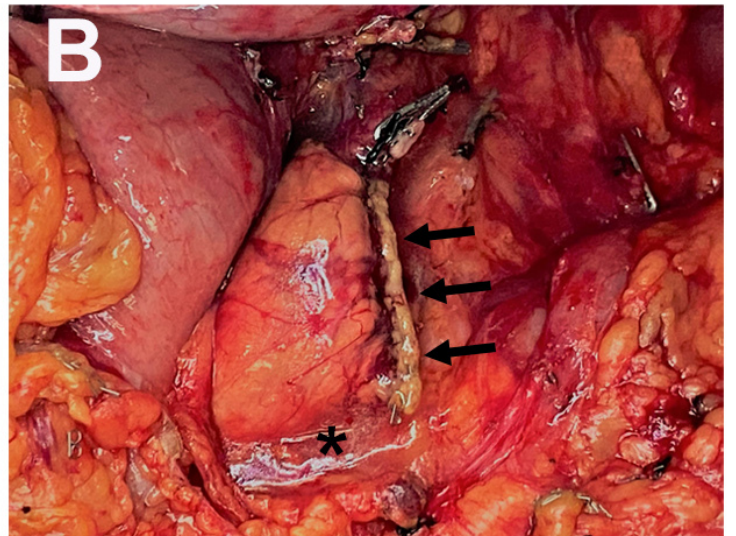
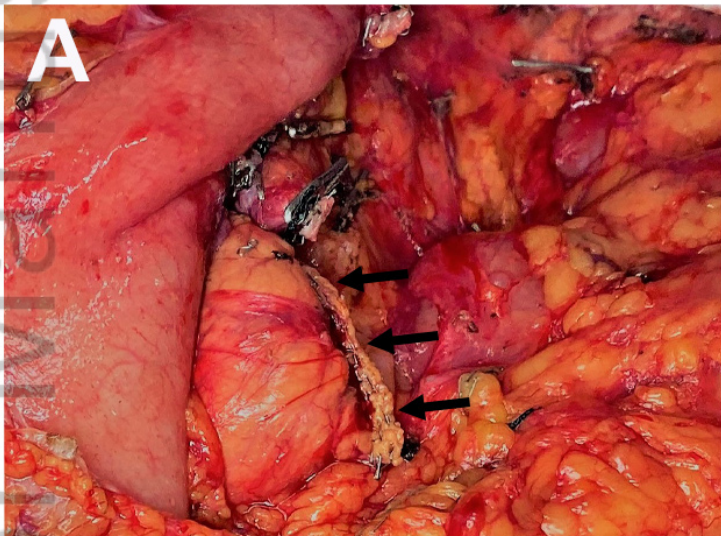
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**Table 1 Characteristics of patients**

	<b>Overall (n=54)</b>	<b>Control group (n=38)</b>	<b>PEG group (n=16)</b>	<b>p - value</b>
<b>Characteristics</b>				
Male	23 (43%)	14 (37%)	9 (56%)	0.19
Age (years)	59 (23 – 82)	53 (23 – 82)	71.5 (33 – 81)	0.07
BMI	26.8 (17.1 – 42.4)	26.6 (17.1 - 42.4)	28.3 (18.7 – 41.0)	0.95
<b>ASA class</b>				
I	4 (7%)	3 (8%)	1 (6%)	0.24
II	20 (37%)	15 (39%)	5 (31%)	
III	26 (48%)	16 (42%)	10 (63%)	
IV	2 (4%)	2 (5%)	0	
<b>Co-Morbidity</b>				
CRF	3 (6%)	2 (5%)	1 (6%)	0.66
Diabetes	14 (26%)	11 (29%)	2 (12.5%)	0.18
Pancreatitis	14 (26%)	8 (21%)	6 (38%)	0.16
COAD	0	0	0	
<b>Laboratory tests</b>				
Haemoglobin (g/L)	139.5 (80 - 165)	137 (80 - 165)	141.5 (114 - 162)	0.33
WCC (x10 <sup>9</sup> /L)	7 (2.9 - 131)	7.7 (2.9 - 141)	6.7 (4.8 - 12.7)	0.42
Platelets (x10 <sup>9</sup> /L)	262.5 (113 - 571)	262 (141 - 571)	265.5 (131 - 488)	0.23
Albumin (g/L)	40 (24 - 46)	39 (24 - 46)	41 (31 - 45)	0.02
Urea (mmol/L)	6 (2.1 - 13.3)	6 (2.1 - 13.3)	6.2 (4.1 - 10.3)	0.34
Creatinine (μmol/L)	71 (20 - 139)	70 (20 - 124)	79.5 (56 - 139)	0.05
BMI – Body mass index, ASA -American Society of Anaesthesiologist classification, CRF – Chronic renal failure, COAD – Chronic obstructive airways disease, WCC – White cell count				

**Table 2. Comparison of operative data**

	<b>Overall (n=54)</b>	<b>Control group (n=38)</b>	<b>PEG group (n=16)</b>	<b>p - value</b>
<b>Operative approach</b>				0.54
Open	37 (69%)	27 (71%)	10 (62%)	
Laparoscopic	17 (31%)	11 (29%)	6 (38%)	
<b>Multi-organ resection</b>				0.02
Spleen	31 (57%)	15 (39%)	16 (100%)	
Liver	7 (13%)	4 (11%)	3 (19%)	
Colon	4 (7%)	1 (3%)	3 (19%)	
<b>Operative time (minutes)</b>	228 (60 – 540)	240 (120 – 540)	175 (60 – 480)	0.02
<b>Operative technique</b>				
Stapled	51 (94%)	35 (92%)	16 (100%)	
Re-enforced staple line	18 (33%)	18 (47%)	0	
<b>Tissue adhesive</b>				
Fibrin	15 (28%)	15 (39%)		
Albumin	3 (6%)	3 (8%)		
Cyanoacrylate	1 (2%)	1 (3%)		
PEG			16 (100%)	
<b>Pathology</b>				
Malignant	30 (56%)	21 (55%)	9 (56%)	0.95
Adenocarcinoma		7 (18%)	4 (25%)	
NET		9 (24%)	2 (13%)	
Other		5 (13%)	3 (19%)	
Benign	24 (44%)	17 (45%)	7 (44%)	
Mucinous cystic		10 (26%)	6 (38%)	
Other		7 (18%)	1 (6%)	
Pancreatitis on histopathology	22 (40%)	15 (39%)	7 (44%)	0.73

PEG – Polyethylene glycol NET – neuroendocrine tumour

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**Table 3. Postoperative complication data**

	<b>Overall (n=54)</b>	<b>Control group (n=38)</b>	<b>PEG group (n=16)</b>	<b>p - value</b>
<b>Length of stay</b>				
Days	9 (4 – 41)	10 (6 – 41)	6 (4 – 14)	0.04
<b>Complications</b>				
Postop complications	19 (35%)	18 (47%)	4 (25%)	0.15
CD 1		7 (18%)	2 (13 %)	0.82
CD 2		4 (11%)	1 (6%)	
CD 3		5 (13%)	1 (6%)	
CD 4		2 (5%)		
<b>All leaks</b>	28 (52%)	25 (65%)	3 (19%)	0.003
Biochemical leak	18 (33%)	16 (42%)	3 (19%)	0.027
<b>POPF</b>				0.045
Grade B	7 (13%)	7 (18%)	0	
Grade C	2 (4%)	2 (5%)	0	
<b>Drain amylase</b>				
Postop day 3 Amylase level	544 (2 – 52744)	916 (4 – 52744)	46 (2 – 3455)	<0.001
<b>Hospital readmission (28 days)</b>	9 (17%)	7 (18%)	2 (13%)	0.71
<b>Mortality (30 days)</b>	0	0	0	

POPF – Postoperative pancreatic fistula. CD – Clavian-Dindo classification.